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## Advances in Alzheimer therapy: understanding pharmacological approaches to the disease

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### Abstract

Although significant accomplishments have been made in research to understand, diagnose and treat Alzheimer's disease (AD) and its prequel, mild cognitive impairment, over the last two decades, a huge amount more remains to be achieved to impact this incurable, terminal disease that afflicts an estimated 26.6 million people worldwide. Increasing evidence indicates that early diagnosis will be fundamental to maximizing treatment benefits. Moreover, mechanistically-based, hypothesis-driven treatment strategies are now emerging to hopefully spearhead future therapy. The cross-fertilization of ideas from multiple disciplines will prove key to optimize strategies and translate them to meaningful clinical utility, and forms the basis of the current issue focused on "Advances in Alzheimer therapy".

The 10th International Hong Kong/Springfield Pan-Asian Symposium on Advances in Alzheimer Therapy, held in Kowloon, Hong Kong, on February 28, 29 and March 1, 2008, for the first time integrated across East and West more than 1200 basic and clinical research scientists/physicians to impart the latest information to unravel the origin and pathogenesis of Alzheimer's disease (AD) and to both discuss and highlight improvements towards its diagnosis and potential treatment by established as well as novel strategies. This unique biennial symposium series continues to provide a priceless mechanism to bring under the same roof a dichotomy of scientific interests and expertise to specifically focus them on AD and related dementias and to disseminate the most current knowledge on recent advances in its potential therapy. AD is now recognized as an incurable, degenerative and terminal disease that is global – afflicting an estimated 26.6 million people worldwide in 2006, with the number growing in an unabated and frightening manner.

In a manner similar to the two prior symposia in this series, the 8th International Montreal/Springfield Symposium published in *Current Alzheimer Research* [1], and the 9<sup>th</sup> International Geneva/Springfield Symposium, likewise, published in *Current Alzheimer*

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*Research* [2], we are pleased to publish selected highlights from the Hong Kong/Springfield Pan-Asia Symposium in the present issue. Our choice of subject matter encompasses an expansive and demonstrative collection of the basic and clinical research that was presented at the Symposium. We challenged each of the authors to generate a forward-looking and provocative article that would be compelling to read for those both in their immediate field and outside of it. We are grateful to have 11 contributions that form the present issue that ably accomplish this. Hence, we are individually beholden to the authors for the value of their articles, their perseverance in under going peer review, and their patience in awaiting publication.

### **Cholinergic based strategies – *what are they, what do they offer and what may the future hold?***

As detailed by Pepeu and Giovannini (page 86–96) the cholinesterase inhibitor (ChEI) drug class was introduced for the symptomatic treatment of AD in 1990s with lofty hopes. Efficacy was anticipated from the ‘cholinergic hypothesis of geriatric memory dysfunction’ and a plethora of preclinical studies in adult, aged and AD transgenic rodents suggest their efficacy derives from augmenting brain acetylcholine (ACh) levels. Wherefore, the now accepted clinical effectiveness of the three widely used ChEIs, donepezil, rivastigmine, galantamine, in mild to moderate AD may potentially derive from this action alone or a combination of this and additional pharmacologic activities remains a matter of opinion, which the authors thoughtfully deliberate. The potential that specific ChEIs may provide valuable actions via mechanisms that are cholinergically as well as non-cholinergically mediated has been proposed. Whether or not the “classical” ChEIs, donepezil, rivastigmine and galantamine, generate such actions beyond their expected cholinesterase inhibition that contribute to their therapeutic efficacy at clinically achievable concentrations is adjudicated. Nevertheless, the authors consider that well-designed multifunctional ChEIs that balance useful and potentially synergistic actions related to disease mechanisms still have a therapeutic role to play, and provide not only a future conduit for cholinergics in AD, but for other indications too, such as mild cognitive impairment, vascular dementia and, possibly, for improvement of memory and learning in healthy subjects.

A recent publication [3] concluded that treatment of dementia with ChEIs and memantine can result in statistically significant but clinically marginal improvement in measures of cognition and global assessment. It is clear that not all patients respond to treatment and yet, on average, some 30 to 60% do even though all have an alike diagnosis of mild to moderate AD. This has led to debate of the economic benefit of current AD treatment (<http://www.nice.org.uk>). Clearly one would expect a variance in drug efficacy between individuals, which may be additionally increased by numerous factors, such as the accuracy of diagnosis, the disease stage and the quality of patient selection, any imprecision, inaccuracy and bias in the neuropsychological measures utilized to assess efficacy, different conformities of research sites to conditions of research protocols as well as numerous other potentially confounding factors [4–7]. Controlling for many of these at a single site, Venneri and colleagues (page 97–111) were able to separate mild AD patients into two groups: ChEI responders and non-responders. Mechanisms underpinning the divergent response of the two

groups to ChEIs were then assessed and compared to a healthy, matched elderly control group utilizing a functional magnetic resonance imaging (MRI) activation paradigm that incorporated semantic association and working memory tasks. An understanding of such mechanisms opens the door to both providing more rational treatment strategies as well as optimizing those currently available.

An alternative approach to augmenting cholinergic neurotransmission by elevating synaptic ACh levels with an anticholinesterase is the use of a direct agonist that is selective for the muscarinic receptor (mAChR) M1 subtype. This is predominantly expressed in the cortex and hippocampus, and remains relatively unchanged in the brain of AD subjects. As described by Caccamo and colleagues (page 112–117) in cellular and in vivo models, the activation of M1 mAChRs with a safe and well-designed selective agonist not only imparts cholinergic-induced improvements in cognition but also activates biochemical cascades involved in the induction and control of both A $\beta$  and tau pathology. This contribution defines the complex interaction between the cholinergic system, A $\beta$  and tau, and reviews the therapeutic promise of M1 agonists as potential disease-modifying agents in AD.

### **Amyloid based strategies – *how can one effectively lower A $\beta$ in a manner that is potentially translatable to the clinic?***

The amyloid hypothesis underpins perhaps the primary strategy of experimental drugs/biologicals currently being developed for the treatment of AD. A $\beta$  accumulation in brain can clearly be elevated by mutations in amyloid- $\beta$  precursor protein (APP), presenilin-1 or -2 (PS1 and PS2, respectively) and other genetic polymorphisms/mutations that can lead to a similar outcome by either chronically increasing the production of A $\beta$ <sub>42</sub> or decreasing its clearance. There are multiple potential points of intervention in such a cascade of events. In this regard, Tian and colleagues (page 118–131) describe the activity of a combination of four herbal extracts, GEPT, to lower brain A $\beta$  levels in APPV717I transgenic mice. Three doses of GEPT were administered orally over an 8-month duration, and compared to transgenic and wild-type saline controls as well as to transgenic mice administered the ChEI, donepezil. In addition to brain A $\beta$ , proteins associated with its generation (BACE1 and PS1), those associated with degradation (insulin-degrading enzyme and neprilysin) were likewise quantified to define mechanisms that underpin the potential promise of this interesting herbal combination.

Whereas the amount of A $\beta$  present in the brain and CSF of AD subjects remains an area of intense interest – particularly with regard to any changes relating to treatment or disease progression, there is escalating attentiveness as to the molecular forms of that A $\beta$ . The contribution of Ito and colleagues (page 132–136) specifically focuses on this facet of A $\beta$  – its ability to self-aggregate and form oligomers: multimeric but non-fibrillar forms of the peptide. Clearly, the structure of a peptide will impact many physicochemical and hence physiological factors that affect its solubility, distribution and biological actions – particularly on synapses that have consistently been noted to be exceptionally vulnerable to multiple forms of A $\beta$ . In this light, Ito and colleagues examined the histochemical localization of oligomer A $\beta$  in AD brains to elucidate its role in the disease process.

Although amyloid plaques are a critical hallmark of AD, the disease plainly involves more than A $\beta$ . Neurofibrillary tangles, the other primary hallmark that are generated from aberrant tau, together with numerous induced secondary factors conjointly impact the disease course. Microglial activation exemplifies a secondary event that can potentially drive the disease process consequent to the release of microglia-derived neurotoxic factors, which can instigate a vicious self-propagating cycle between up- and downstream processes. Imaging and quantifying these in living brain to elucidate their interactions during disease progression as well as treatment strategies is the topic of the contribution by Makoto Higuchi (page 137–143). The brains of AD transgenic mice were examined by high-resolution positron emission tomography (PET) following administration of specific probes for amyloid, tau and microglial activation as neuroimaging biomarkers to follow these events in living brain.

An early hypothesis-driven clinical trial that, in large part, aimed to test the amyloid hypothesis was the immunization of AD patients with synthetic A $\beta$ <sub>42</sub> (AN1792) in a randomized, double-blind, placebo-controlled phase 2a study. In prior preclinical studies, immunotherapy with human A $\beta$ <sub>42</sub> stimulated the clearance of amyloid plaques and reduced AD-associated cognitive declines in mouse model of AD. Albeit that the AN1792 trial was halted following reports of encephalitis, it has nevertheless provided a wealth of valuable information. Vellas and colleagues (page 144–151) add to this in an analysis of subjects from the original trial some 4.6 years after immunization in which multiple measures were undertaken to determine both cognitive and pathological differences between AN1792 antibody responders and placebo-treated patients.

### **Tau based strategies – *an invariable feature of AD and a drug target to impeded disease progression***

Other crucial hypothesis-driven strategies to slow or potentially halt the progression of AD are being developed as, likely, a combination of approaches may ultimately prove most effective, as found in other diseases. The hyperphosphorylation of tau in AD brain, leading to the development of neurofibrillary tangles, is an unambiguous feature of AD and the focus of several therapeutic strategies. Comprehending the complex interactions between aberrant tau aggregation, synaptic loss and cholinergic system dysfunction is fundamental in understanding the disease process and developing viable intervention approaches. This is the focus of the contribution provided Belarbi and colleagues (page 152–157), who have developed a THY-Tau 22 transgenic mouse model that reliably recapitulates the Alzheimer-type neurofibrillary degeneration in the absence of amyloid deposits. This mouse develops age-dependent tau pathology that leads to synaptic dysfunction and impairments in learning and memory, and is utilized by the authors to elucidate tau/cholinergic system relations.

### **Novel approaches to augment the cholinergic system – *exquisitely vulnerable and absolutely vital***

Trophic support is indispensable to the health and survival of many types of neurons, and particularly for cholinergic ones. As described by Covaceuszach and colleagues (page 158–

170), the neurotrophin family member, nerve growth factor (NGF), exerts a wide and crucial range of physiological actions on basal forebrain cholinergic neurons, which constitute its primary target. The basal forebrain cholinergic system provides key projections to the cerebral cortex and hippocampus that support learning and memory, but appears particularly vulnerable to disruption in AD. Augmenting NGF has, hence, provided an attractive therapeutic option to preserve or rescue the cholinergic system in AD, but safely and effectively enacting this strategy has proved difficult. In this light, Covaceuszach and colleagues describe an engineered mutein of human (h)NGF, hNGF-61, that is bio-equivalent to but can be differentiated from hNGF, to make it traceable and thereby facilitate the determination of optimal dosing and distribution. The efficacy of hNGF-61 is described in an AD mouse model following its non-invasive intranasal administration.

### **New models and diagnostics – *opening new windows to understand the basis of, diagnose and treat AD***

Although AD is clearly a human neurodegenerative condition, rodents, and in particular transgenic mice expressing human proteins relevant to the disease and occasionally with specific proteins deleted, have proved to be powerful tools to both aid elucidate molecular mechanisms underpinning the disease process and to assess the potential efficacy of therapeutic interventions. In this light, Sarasa and Pesini (page 171–178) provide interesting insight as to how specific natural non-transgenic animal models could valuably contribute to AD research and drug development. Notably, the chick embryo and the dog have, among numerous attributes, an enzymatic machinery for processing APP that is almost identical to that of humans. The authors review the characteristics and potential utility of a wide array of natural models, which with versatility replicate particular aspects of AD, and could aid in moving the field forward on several fronts.

To optimally assess the efficacy of a disease modifying therapeutic strategy one must utilize it early, rather than late, in a disease process, as has been demonstrated in other conditions epitomized by cancer and heart disease. Early diagnosis is thus key. As reviewed by Pihlajamäki and colleagues (page 179–185), the reliable early diagnosis of AD, however, is one of the most interesting as well as challenging areas of current AD research. The identification of individuals with prodromal AD – mild cognitive impairment (MCI), and in particular the amnesic subtype of MCI, representing an intermediary state between normal aging and clinical AD in which memory impairment is subtle and structural atrophy insignificant - would provide subjects with sufficient conserved function remaining. It is in this frontier area that structural and functional MRI are making inroads to provide the tools required to select out and follow the disease process.

In closure, this issue captures a window, in the form of 11 stimulating articles, of a thought-provoking symposium focused not only on the latest advances in AD research, diagnosis and treatment but also on identifying the most critical gaps in our knowledge that require filling. We are appreciative of the numerous scientists that aided in the peer-review process and wish to thank the organizers of the meeting, sponsors and publisher and staff of *Current*

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